Tegsedi (inotersen)
Policy Number: C17325-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
6/1/2019	6/3/2020	6/3/2021
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J3490 (NOC)	RxPA	Q3 2020 20200722C17325-A

PRODUCTS AFFECTED:
Tegsedi (inotersen)

DRUG CLASS:
Antisense Oligonucleotide

ROUTE OF ADMINISTRATION:
Subcutaneous injection

PLACE OF SERVICE:
Specialty Pharmacy

AVAILABLE DOSAGE FORMS:
Tegsedi Injection: 284 mg/1.5mL single-dose prefilled syringe (pack of 1 or pack of 4)

FDA-APPROVED USES:
Tegsedi is indicated for treatment of polyneuropathy from hereditary transthyretin-mediated (hATTR) amyloidosis in adults.
E85.1 Neuropathic heredofamilial amyloidosis

COMPENDIAL APPROVED OFF-LABELED USES:
None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
Polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis

REQUIRED MEDICAL INFORMATION:
A. POLYNEUROPATHY OF HEREDITARY TRANSTHYRETIN-MEDIATED (hATTR) AMYLOIDOSIS:

1. Documented diagnosis of polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis
   AND
2. Documentation of ONE of the following: (a) Member has a baseline hATTR amyloidosis Stage 1 or 2; OR (b) Member has a baseline polyneuropathy disability (PND) score < IIIb; OR (3) Member has a baseline neuropathy impairment (NIS) score > 10 and < 130
   AND

3. Documentation of a TTR mutation through genetic testing (e.g., V30M)
   AND
4. Submission of ALL of the following lab results: (a) platelet counts (> 100 x 10^9/L), (b) renal function status (serum creatinine, urinary protein to creatinine ratio (UPCR), urinalysis), AND (c) liver function tests (ALT, AST, bilirubin). Refer to "Other Special Considerations" section
   AND
5. Documentation that member does NOT have ANY of the following conditions: New York Heart Association (NYHA) class III or IV heart failure; OR History of liver transplantation; OR History of severe renal impairment or end-stage renal disease; OR Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis
   AND
6. Member has tried and failed or is concurrently taking ONE formulary medications from at least ONE of the following pharmacologic classes for symptoms of polyneuropathy: gabapentin (e.g.; gabapentin), anticonvulsant (e.g., pregabalin), tricyclic antidepressant (e.g.; nortriptyline, amitryptyline) OR Serotonin/Norepinephrine Reuptake Inhibitors (e.g., duloxetine)
   AND
7. Prescriber attests that member will not be using Tegsedi in combination with any the following agents: Onpattro (patisiran), tafamidis or diflunisal
   AND
8. Prescriber attests that if female and of child-bearing potential, member is non-pregnant, nonlactating, and will use appropriate contraception- If male and engaged in relations of childbearing potential, member will use appropriate contraception
   AND
9. Documentation that if previously treated with tafamidis, member has discontinued treatment for 2 weeks prior to initiation of Tegsedi OR If previously treated with diflunisal, member has discontinued treatment for 3 days prior to initiation of Tegsedi

DURATION OF APPROVAL:
Initial authorization: 3 months, continuing authorization: 12 months

QUANTITY:
284 mg/1.5mL single-dose prefilled syringe per week

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in treatment of amyloidosis. Prescriber and member are enrolled in the Tegsedi REMS program

AGE RESTRICTIONS:
18 years of age and older

CONTINUATION OF THERAPY:
A. POLYNEUROPATHY OF HEREDITARY TRANSTHYRETIN-MEDIATED (hATTR) AMYLOIDOSIS:

1. Member has previously received treatment with Tegsedi
   AND
2. Documentation of a positive response to therapy using Tegsedi (e.g., improved neurologic impairment, motor function, slowing of disease progression, cardiac parameters etc.)
   AND
3. Prescriber attests to continued appropriate monitoring for signs or symptoms of thrombocytopenia, glomerulonephritis and other serious side effects

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Tegsedi (inotersen) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Other labeled contraindications include members with platelet counts <100 x 10^9/L, a history of acute glomerulonephritis caused by Tegsedi, and a history of a hypersensitivity reaction to Tegsedi.

A black-box-warning exists for thrombocytopenia, and glomerulonephritis.

OTHER SPECIAL CONSIDERATIONS:

Tegsedi is available only through a Risk Evaluation and Mitigation Strategy (REMS) called the Tegsedi REMS Program due to risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis. Both member and prescriber must be enrolled in this program.

Tegsedi treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for members taking Tegsedi.

Monitoring:

Platelets: At baseline, as necessary throughout treatment and for 8 weeks (or longer if platelet counts remain <100,000/mm^3) following the discontinuation of treatment. Inotersen is contraindicated in patients with a platelet count below 100,000/mm^3

Serum creatinine, eGFR, urine protein to creatinine ratio, urinalysis: Inotersen should not be given to patients who develop a UPCR of 1,000 mg/g or higher, or eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause

AST, ALT, total bilirubin: Monitor at baseline, every 4 months during treatment, and for 8 weeks following the discontinuation of treatment. In liver transplant patients, monitor at baseline, monthly during treatment, and for 8 weeks following the discontinuation of treatment

BACKGROUND:

Hereditary transthyretin (hATTR) amyloidosis is a rare, progressive and debilitating disorder caused by a genetic mutation in the transthyretin (TTR) gene. Transthyretin (TTR) is a protein primarily produced in the liver and secreted into plasma to transport thyroxine (T4) retinol and (vitamin A). Mutations in the TTR gene lead to de-stabilization, misfolding and aggregation into insoluble amyloid fibrils which deposit into multiple sites such as the nervous system, heart, kidneys, and eyes. There are multiple TTR mutations, the most prevalent being TTR V30M. Common symptoms of hATTR amyloidosis include peripheral sensory or autonomic neuropathy, cardiomyopathy, and GI dysfunction.2 As the disease progresses, symptoms can worsen and lead to life-threatening multiorgan dysfunction.

Given the magnitude of non-specific symptoms, diagnosis of hATTR is often challenging and is commonly confused with other conditions. Treatment options include liver transplantation and a limited number of pharmacologic therapies. While liver transplantation has been shown to eliminate the production of variant TTR protein and slow disease progression, it does not prevent cardiomyopathy as amyloids can continue to deposit in the heart.3 One treatment option is Vyndaqel (tafamidis), a transthyretin stabilizer, which stabilizes the tetramer of the TTR transport protein to slow the dissociation into monomers that drives TTR amyloidosis. Vyndaqel is indicated for the treatment of cardiomyopathy of wild type or hATTR amyloidosis. Recently approved treatment options for polyneuropathy of hATTR amyloidosis involve inhibition of hepatic production of TTR using a gene silencing RNA molecule, Onpattro (patisiran), and an antisense oligonucleotide, Tegsedi (inotersen).

Tegsedi (inotersen) binds to and degrades the mutant and wild-type TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. The FDA approved Tegsedi in October 2018 based on data from the NEURO-TRR study, a 66-week placebo-controlled, phase 3 trial with primary efficacy endpoints being mean change in baseline of the Modified Neuropathy Impairment Score+7 (mNIS+7) and the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score (see Appendix A and B). Participants of this study were between the ages of 18-82 years old with a diagnosis of stage 1 or 2 hATTR amyloidosis, a Neuropathy Impairment Score (NIS) between 10 – 130, a TTR mutation, and amyloid deposits confirmed through biopsy. Key exclusion criteria included NYHA Class III or higher, previous liver transplant, presence of DM associated neuropathy, and chronic kidney disease. The NEURO-TRR study showed Tegsedi to improve the course of neurologic disease in the quality of life in members with hATTR amyloidosis. Both primary endpoints showed significant benefits with Tegsedi treatment when compared to placebo.

APPENDIX:

A. Scoring Scale of Mnis+7 (the higher the score, the less function)

A) mNIS+7

Test	Component	Minimum Score	Maximum Score
NIS	Cranial Nerves	0	40
	Muscle Weakness	0	152
	Reflexes	0	20
	Sensation	0	32
Modified +7	Heart Rate Deep Breathing†	-3.72	3.72
	Nerve Conduction†	-18.6	18.6
	Touch Pressure	0	40
	Heat-Pain	0	40
mNIS+7*	**Composite**	**-22.3**	**346.3**

B. Scoring Scale of Norfolk QoL-DN (the higher the score, the poorer the quality of life)

B) Norfolk QoL-DN

Domain	Items[1,2]	Minimum Score	Maximum Score
Symptoms	Σ (1-7, 9)	0	32
Physical Functioning/Large Fiber Neuropathy	Σ (8, 11, 13-15, 24, 27-35)	-4	56
Small Fiber Neuropathy	Σ (10, 16-18)	0	16
Large Fiber Neuropathy	Σ (19-21)	0	12
Activities of Daily Living	Σ (12, 22, 23, 25, 26)	0	20
Norfolk QoL-DN*	**Total**	**-4**	**136**

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, member records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

REFERENCES:

1. Tegsedi (inotersen) [package insert]. Boston, MA: Akcea Therapeutics, Inc.; October 2019
2. Ando, Y., Coelho, T., Berk, J. L., Cruz, M. W., Ericzon, B. G., Ikeda, S., N Salvi, F. (2013). Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet journal of rare diseases*, *8*, 31. doi:10.1186/1750-1172-8-31
3. Gales, L. (2019). Tegsedi (Inotersen): An Antisense Oligonucleotide Approved for the Treatment of Adult Members with Hereditary Transthyretin Amyloidosis. *Pharmaceuticals*, *12*(2), 78. doi:10.3390/ph12020078
4. Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. Institute for Clinical and Economic Review. August 29, 2018